Panel 4: Treatment

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Timeline of Anticoagulation Options
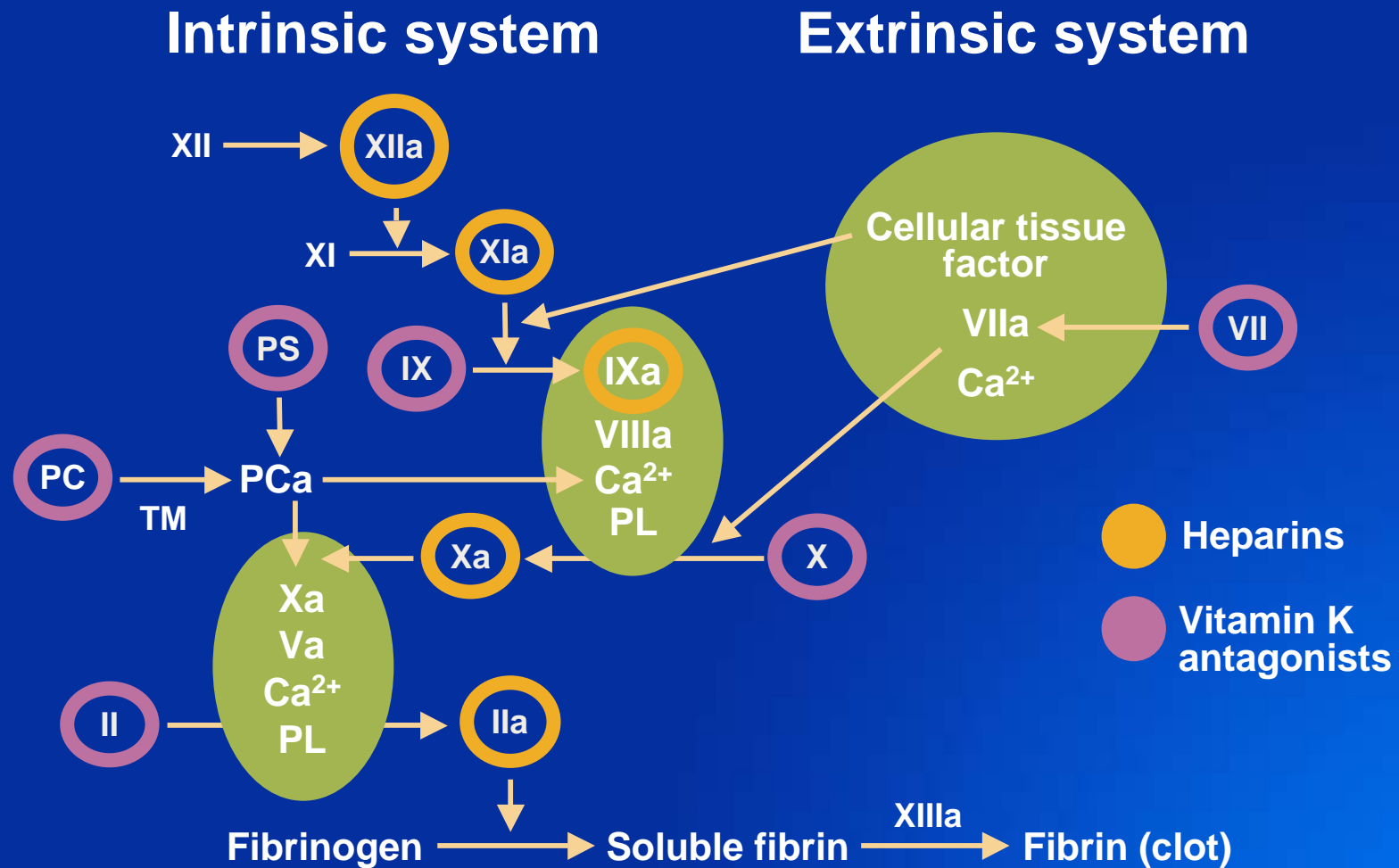
1916	1950s	1970s	1990s	2002

Heparin   **Warfarin**   **LMWH**   **Selective factor Xa inhibitor**

Direct thrombin inhibitors
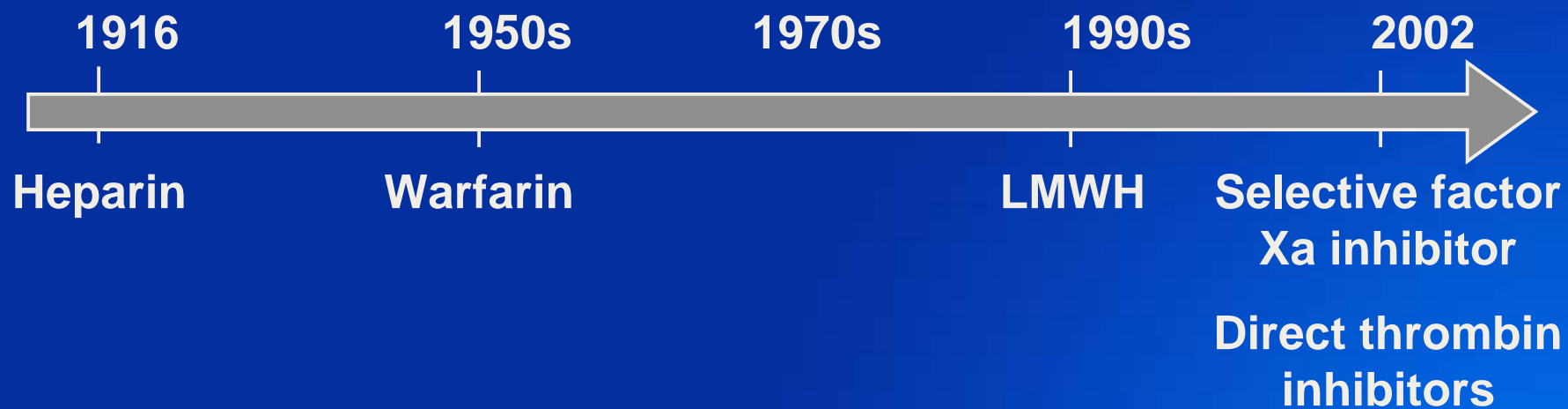
Weitz J, Hirsh J. *Chest.* 2001;119:95S.

Current Anticoagulants

	Route of Administration	Laboratory Monitoring
Heparin	Parenteral	Yes
Low molecular weight heparins	Parenteral	No
Fondaparinux	Parenteral	No
Direct thrombin inhibitors	Parenteral	Yes
Vitamin K antagonists (warfarin)	Oral	Yes

Current antithrombotic agents: multi-targeted

Intrinsic system

Extrinsic system

XII → XIIa

XI → XIa

PS

IX

PC → PCa

TM

Xa
Va
Ca^{2+}
PL

II

IIa

IXa
VIIIa
Ca^{2+}
PL

Cellular tissue factor
VIIa
Ca^{2+}

VII

X

Xa

Fibrinogen → Soluble fibrin — XIIIa → Fibrin (clot)

Heparins

Vitamin K antagonists

Advantages of LMWH over UFH

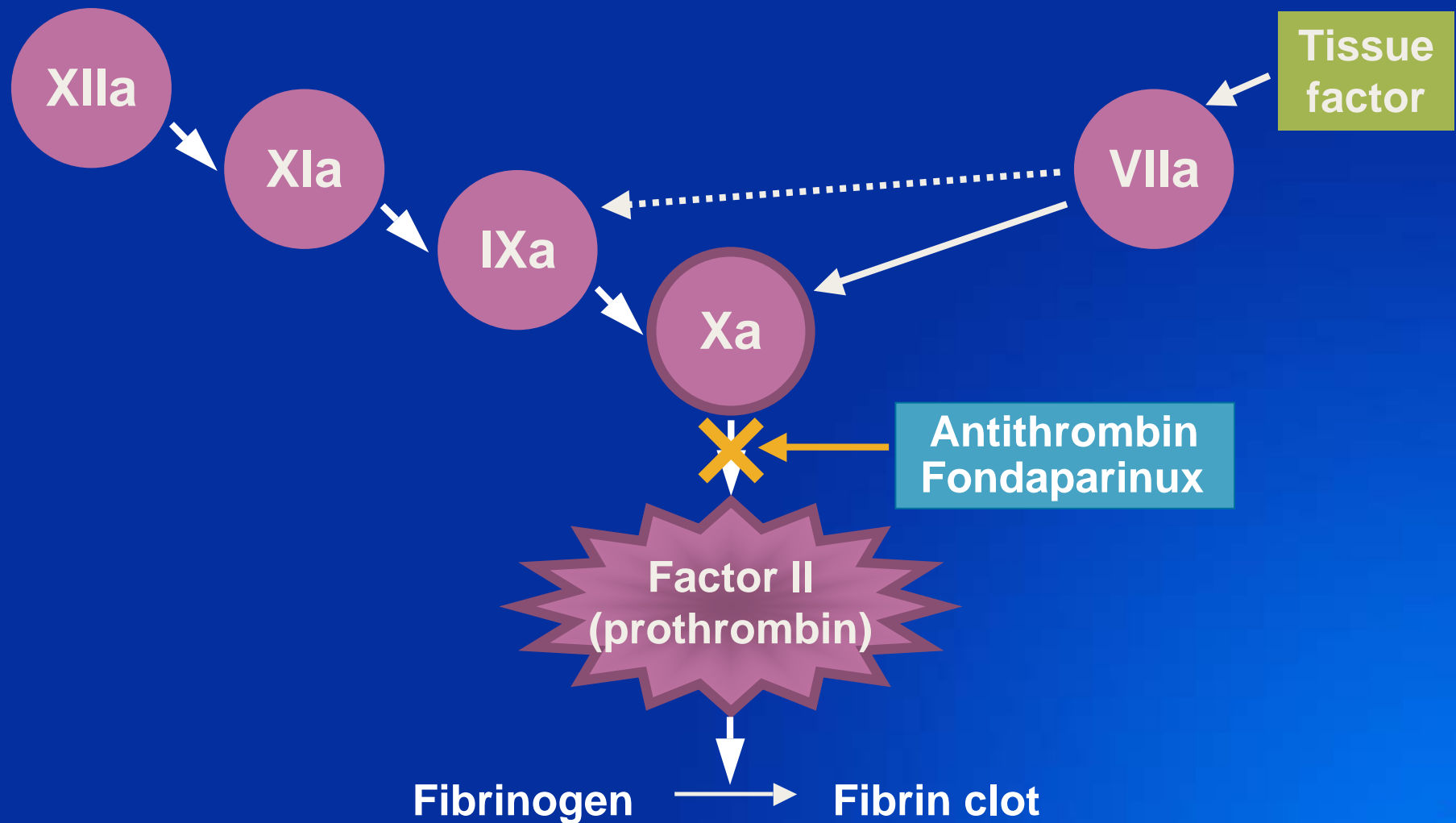Better bioavailability and predictable pharmacokinetics

$\Rightarrow$ VTE treatment using weight-based dosing with no need for laboratory monitoring

Longer half-life

$\Rightarrow$ twice or once daily subcutaneous dosing

Lower rate of heparin-induced thrombocytopenia

Fondaparinux

- Synthetic pentasaccharide

- Longer half-life than LMWH

- No laboratory monitoring required

- No reactivity with HIT antibodies

- Approved for prophylaxis of VTE following major orthopedic and abdominal surgery and for treatment of VTE

Limitations of Warfarin
(Vitamin K Antagonists)

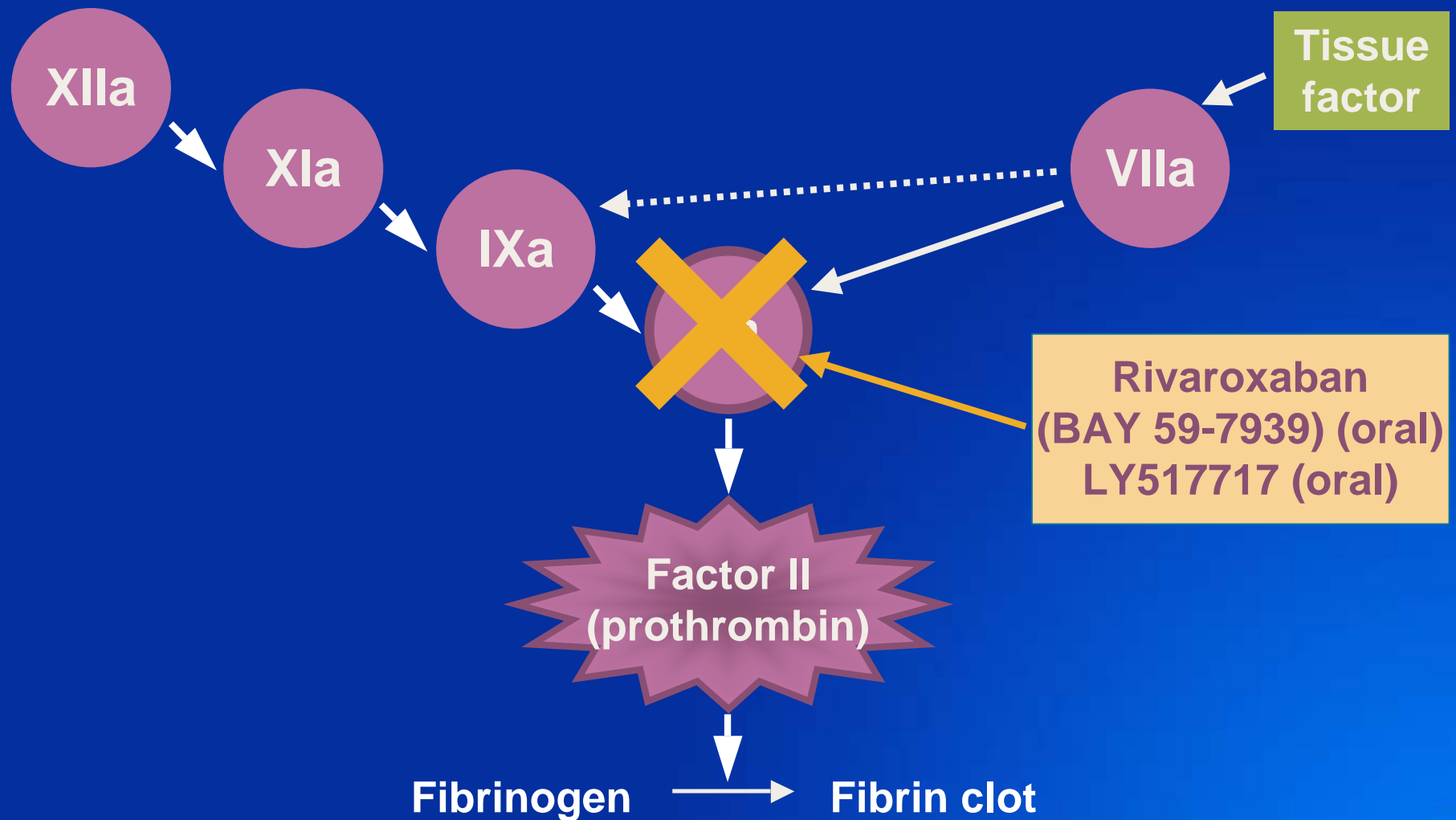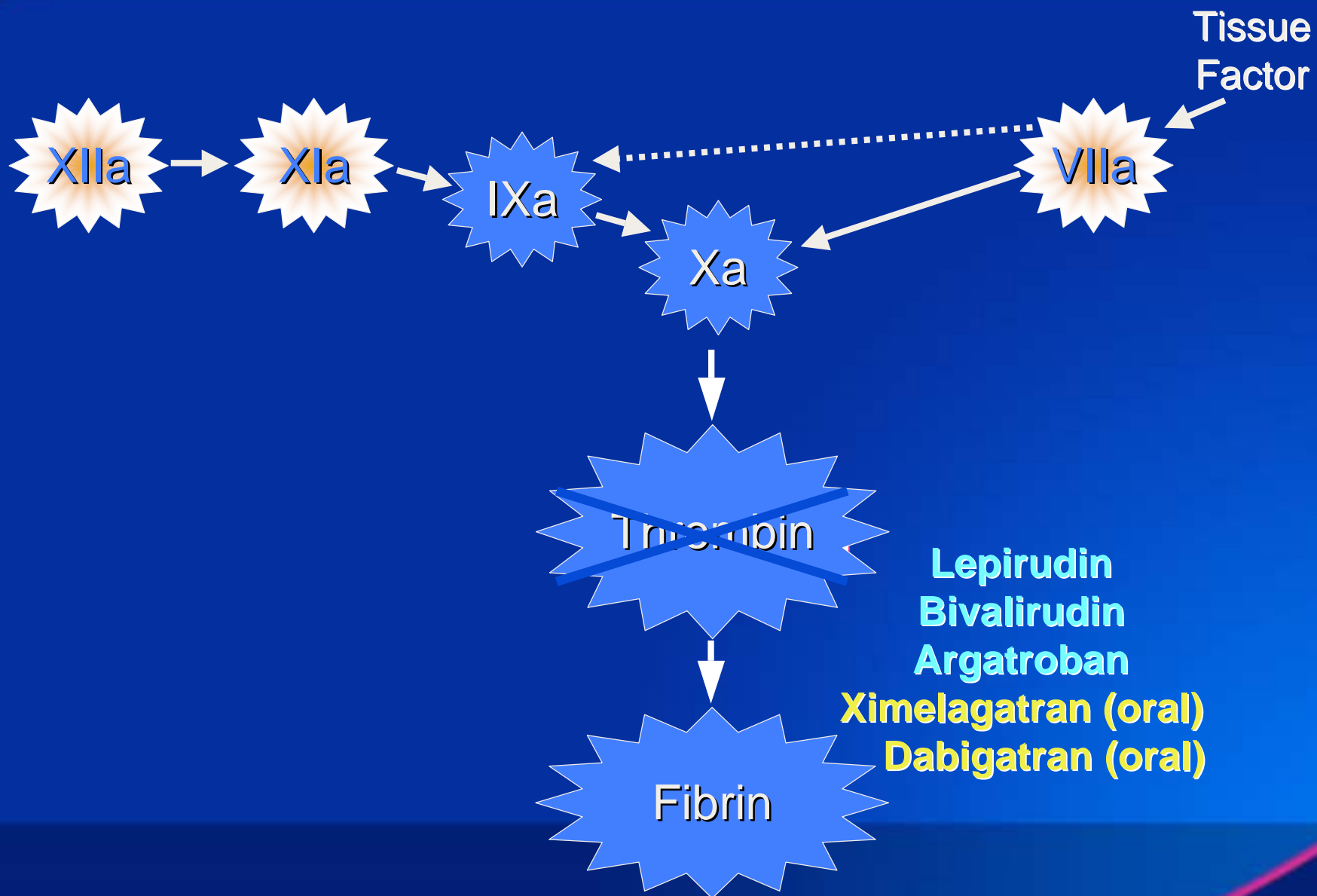| LIMITATION	CONSEQUENCE
Slow onset of action	Overlap with a parenteral anticoagulant
Genetic variation in metabolism	Variable dose requirements
Multiple food and drug interactions	Frequent coagulation monitoring (INR)
Narrow therapeutic index	Frequent coagulation monitoring (INR)

Anticoagulant Treatment of Venous Thromboembolism

1. Initial treatment with adequate doses of heparin is important.

2. Warfarin can be initiated early.

3. Antithrombotic effect of warfarin requires reduction of prothrombin levels: this effect requires at least 4 days of treatment and the need for overlap with heparin.

4. DVT can be treated at home with LMWH/fondaparinux.

5. Unprovoked ("idiopathic") VTE is a chronic disease.

6. What is the optimal duration of initial treatment? Which patients require long term anticoagulant therapy and what should the INR intensity be?

Recurrent Venous Thrombosis is Common Following a First Episode of Symptomatic DVT

Prandoni et al, Ann Intern Med 1996;125:1-7
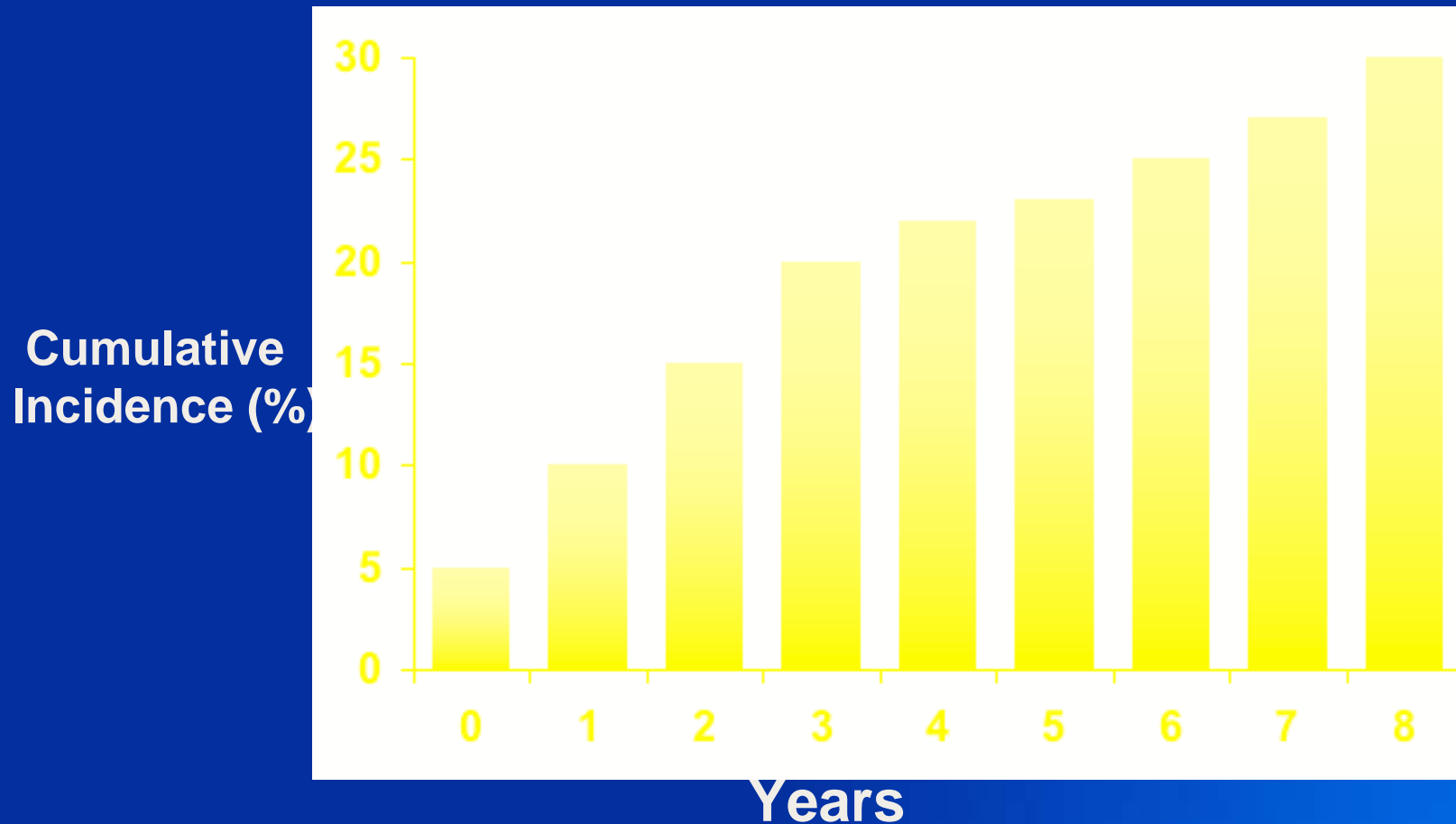
Duration of Anticoagulant Therapy

- First event with reversible or time limited risk factor
  - 3-6 months at INR 2-3

- Unprovoked VTE, first or second event
  - 6-12 months at INR 2-3, then consider

    indefinite anticoagulation at INR 2-3 weighing recurrence versus bleeding risk (? INR 1.5-2)

- Special Situations - indefinite anticoagulation
  - First event with
    - Cancer until resolved (consider chronic LMWH)
    - Antiphospholipid antibody syndrome
    - Antithrombin deficiency or multiple genetic defects,

      ? deficiencies of protein C or protein S